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Fever in ICU Patients: Clinical Challenges and Management

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Abstract

Background: Fever is a common and clinically significant finding in intensive care units (ICUs), often signaling infection but also arising from diverse non-infectious etiologies. Its interpretation is complex due to critical illness physiology, invasive interventions, and immune variability.

Aim: To review the definitions, epidemiology, pathophysiology, diagnostic approach, and management strategies for fever in critically ill patients, emphasizing evidence-based practices and context-specific considerations.

Methods: A comprehensive narrative review of current guidelines and major epidemiologic studies was conducted, integrating data on fever thresholds, etiologic patterns, diagnostic algorithms, and therapeutic interventions in ICU settings.

Results: Fever occurs in 26–88% of ICU patients, with sepsis accounting for approximately 63% of cases. Infectious causes include ventilator-associated pneumonia, catheter-related bloodstream infections, and intra-abdominal infections, while non-infectious sources range from drug fever to thromboembolic disease and endocrine crises. High-grade fever (>39.5°C) correlates with increased mortality, particularly in non-septic patients. Diagnostic evaluation requires systematic history, physical examination, microbiologic sampling, biomarker interpretation, and imaging. Management prioritizes early antimicrobial therapy, source control, and individualized temperature regulation. Evidence does not support routine aggressive fever suppression except in neurologic injury or extreme hyperthermia.

Conclusion: Fever in ICU patients is a multifactorial phenomenon requiring disciplined evaluation and tailored management. Over-reliance on fever as an infection surrogate risks unnecessary antibiotic use and missed alternative diagnoses. Optimal care integrates rapid infection control, judicious antipyresis, and multidisciplinary collaboration.

Keywords: Fever, Intensive Care Unit, Sepsis, Hyperthermia, Antipyretics, Diagnostic Evaluation, Source Control

Introduction

Body temperature is a core physiological parameter and an indispensable vital sign in the assessment and ongoing monitoring of all hospitalized patients, particularly those managed in intensive care units (ICUs). In this environment, even modest deviations from thermal homeostasis frequently trigger a cascade of clinical responses, including repeated bedside examination, expanded diagnostic evaluation, and timely modification of therapeutic strategies. The ICU context amplifies the significance of temperature abnormalities because critically ill patients often demonstrate rapid clinical transitions, limited physiologic reserve, complex multisystem dysfunction, and frequent exposure to invasive devices and interventions. Consequently, fever and hypothermia are not merely descriptive findings in intensive care practice; rather, they are clinically consequential signals that may reflect evolving pathophysiology, iatrogenic complications, or shifts in host–pathogen dynamics, each of which may demand prompt interpretation and action [1]. Importantly, the operational definition of fever in critically ill patients is not identical to the conventional thresholds used in less acute settings. In the ICU, the definition is intentionally standardized to enhance diagnostic consistency and to reduce unnecessary testing in a population where temperature variation can be influenced by numerous confounders. According to the American College of Critical Care Medicine (ACCCM) and the Infectious Disease Society of America (IDSA) joint task force, fever in an ICU patient is defined as a single recorded temperature of at least 101°F (≥38.3°C).[1] In

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alignment with this definition, the same expert bodies advise that a diagnostic workup for fever in the ICU should generally be initiated only when the temperature reaches or exceeds this threshold.[1] This guidance reflects a pragmatic balance: it recognizes the high prevalence of low-grade temperature elevations in critically ill patients—many of which are nonspecific or transient—while prioritizing investigation when the probability of clinically relevant infection or inflammatory pathology becomes more substantial. At the extreme end of the thermal spectrum, hyperpyrexia or hyperthermia is characterized by temperatures exceeding 105.8°F (41°C). Such presentations are relatively uncommon in intensive care practice, yet they represent a potentially life-threatening physiologic state, often associated with distinct etiologic categories and urgent therapeutic priorities compared with routine febrile syndromes [1].

The interpretation of fever thresholds must be further refined in immunocompromised populations, particularly among patients with neutropenia, because the host inflammatory response can be attenuated or atypical. In these patients, a lower clinical threshold for recognizing and treating fever is warranted, given that they may fail to mount a robust febrile response even in the presence of severe infection. Moreover, the expected clinical, laboratory, and radiologic signs of inflammation may be minimal or absent early in the disease course, delaying recognition unless clinicians maintain heightened vigilance. Within this vulnerable subgroup, fever in a neutropenic ICU patient is defined either as a single temperature above 101°F (38.3°C) or as a temperature exceeding 100.4°F (38.0°C) sustained for more than one hour, in the setting of an absolute neutrophil count (ANC) below 500 cells/mm³.[2][3] These criteria emphasize both the lower temperature threshold and the temporal dimension of fever in neutropenia, recognizing that sustained low-grade elevations may carry comparable clinical significance to isolated higher spikes in patients capable of normal inflammatory signaling. In addition to immunologic factors, clinicians must also account for extracorporeal and device-related influences on temperature measurement and physiologic heat exchange. Therapies such as continuous renal replacement therapy and extracorporeal membrane oxygenation may blunt, obscure, or otherwise modify the febrile response by altering heat loss, modulating cytokine profiles, or affecting measurement accuracy. As a result, the absence of fever in patients receiving such therapies should not be interpreted simplistically as reassurance against infection, especially when other features of clinical deterioration are present. From an evolutionary and immunological perspective, fever is generally understood as an adaptive host response that may confer protective benefits. The elevation of body temperature can inhibit pathogen replication, enhance leukocyte function, and augment the efficiency of immune signaling, thereby contributing to the elimination of invading organisms. Despite these plausible physiologic advantages, fever in critically ill patients is also associated with increased morbidity and mortality, and it is incorporated into widely used mortality prediction instruments such as APACHE II and APACHE III. Yet, the relationship between fever and outcomes in ICU populations has not been consistently defined across studies, in part because fever is not a uniform exposure but rather a heterogeneous manifestation shaped by underlying diagnosis, immune status, treatment interventions, and timing within the illness trajectory. In other words, fever may represent a marker of disease severity in some contexts, a beneficial immune response in others, or an epiphenomenon related to noninfectious stressors or clinical care [1].

The ambiguity in outcome associations is illustrated by major epidemiologic investigations. A large study published in 2008 reported that temperatures at or above 39.5°C were associated with increased mortality among critically ill patients, whereas the mere presence of fever defined by a threshold of at least 38.3°C did not demonstrate a clear association with mortality.[4] This finding suggests that only higher-grade fever may function as a prognostic indicator of adverse outcomes in unselected ICU cohorts, while lower-grade temperature elevations may be too nonspecific to carry meaningful predictive value. Subsequent work has further nuanced this relationship. The FACE study, published in 2012, found that the increased 28-day mortality associated with temperatures at or above 39.5°C was observed in non-septic patients rather than in those with sepsis.[5] This observation challenges simplistic interpretations of fever as universally harmful and suggests that fever may have different implications depending on the underlying syndrome driving critical illness. In sepsis, for example, fever could reflect a relatively preserved host response, whereas in non-septic critical illness it may signify uncontrolled inflammation, neurologic injury, drug reactions, or other processes with distinct prognostic meaning. Adding to this complexity, some investigations have described an inverse association between fever and mortality among ICU and emergency department patients, implying that the presence of fever in certain circumstances may correlate with improved survival.[6][7] Such findings can be interpreted as supporting the possibility that a febrile response, when appropriately generated, may indicate intact immunologic competence or more favorable host physiology, particularly when contrasted with afebrile presentations of severe infection or systemic inflammation where immune paralysis or impaired thermoregulation may prevail. Within the ICU, fever should therefore be approached

as a clinical sign with a broad differential diagnosis and context-dependent significance rather than as a singular surrogate for infection. In many cases, elevated temperature represents the continuation of the pathologic process that precipitated ICU admission, such as pneumonia, intra-abdominal infection, pancreatitis, central nervous system injury, or systemic inflammatory disorders. In other instances, fever arises from etiologies that are more characteristic of the ICU milieu, shaped by the intensity of monitoring, the frequency of invasive procedures, the use of indwelling catheters, and the exposure to medications and supportive technologies. ICU-acquired fever may result from infections related to devices or procedures, inflammatory reactions to transfusions, drug fever, thrombosis, atelectasis-associated inflammation, or other noninfectious inflammatory states. Additionally, critically ill patients can develop new-onset fever driven by systemic inflammatory response syndrome, septic physiology, metabolic derangements, or neuroendocrine dysregulation, all of which may occur independently of an identifiable pathogen. Although comparatively rare, fever may also reflect the unmasking or exacerbation of a previously dormant disease or chronic inflammatory condition, particularly as critical illness and its therapies alter immune function and physiologic equilibrium [1][2][3].

This review focuses predominantly on fever in ICU patients who are neither neutropenic nor otherwise profoundly immunocompromised, given that the diagnostic thresholds, risk stratification, and empiric management priorities differ substantially in those high-risk groups.[2][3] Nevertheless, it is important to acknowledge that ICU populations are not neatly partitioned into mutually exclusive categories and overlap in clinical presentation and management principles is common. For example, the evaluation of an unexplained fever must consider infectious and noninfectious etiologies across all patient types, while simultaneously incorporating patient-specific modifiers such as immunologic status, recent interventions, and the presence of extracorporeal support. Accordingly, a disciplined, context-aware approach to fever in the ICU remains essential: one that recognizes standardized definitions and thresholds,[1] appreciates the variable prognostic implications suggested by epidemiologic evidence,[4][5] and remains responsive to the heterogeneity of mechanisms that can produce fever in the critically ill.[6][7]

Etiology

The causes of fever in the intensive care unit are broadly categorized into infectious and non-infectious origins, and in clinical practice the distinction is often initially probabilistic rather than definitive. Although critically ill patients may develop temperature elevation from a wide spectrum of inflammatory and dysregulated physiologic states, infections remain the dominant driver of febrile episodes in the ICU. This predominance reflects the convergence of multiple risk factors that are inherent to critical illness and intensive care delivery, including impaired host defenses, disruption of normal anatomic barriers, frequent exposure to invasive devices, repeated procedures, and prolonged hospitalization. In a multicenter prospective observational study, sepsis accounted for fever in approximately 63% of critically ill patients who developed a febrile episode, underscoring the substantial likelihood of an infectious etiology when fever emerges in this setting.[7] Nevertheless, a significant proportion of ICU fevers arise from non-infectious mechanisms, and over-attribution of fever to infection can lead to unnecessary antimicrobial exposure, avoidable diagnostic testing, and delayed recognition of alternative life-threatening processes. Infectious etiologies of fever in the ICU often reflect either primary infections present at admission or secondary infections acquired during the course of critical care. Among the most frequent causes are ventilator-associated pneumonia, catheter-related bloodstream infections, surgical site infections, catheter-associated urinary tract infections, and bacteremias from diverse sources, including those originating from the respiratory tract, urinary tract, intra-abdominal compartments, skin and soft tissue, or intravascular devices. The ICU environment increases the risk of such infections both by concentrating vulnerable hosts and by necessitating the very interventions that stabilize physiology yet create portals of entry for microorganisms. For example, mechanical ventilation—while lifesaving—bypasses upper airway defenses, facilitates microaspiration around endotracheal cuffs, and can enable biofilm formation, collectively increasing susceptibility to ventilator-associated pneumonia. Similarly, intravascular catheters provide essential access for vasoactive drugs, parenteral nutrition, and hemodynamic monitoring, but can also serve as a nidus for colonization and bloodstream invasion, leading to catheter-related bloodstream infections. Indwelling urinary catheters simplify output measurement and bladder management but raise the likelihood of catheter-associated urinary tract infection, particularly with prolonged duration and breaks in closed drainage systems [7].

A useful framework for considering infectious fever is to organize likely sources by organ system and clinical context. Central nervous system infections such as meningitis, encephalitis, and brain abscess are important considerations, particularly in patients with altered mental status, seizures, focal neurologic deficits, head trauma, neurosurgical procedures, cerebrospinal fluid diversion devices, or immunosuppression. These infections can progress rapidly and may present subtly in sedated or mechanically ventilated patients, where classic clinical signs such as nuchal rigidity or headache are

not readily elicited. Respiratory tract infections remain among the most common infectious drivers of fever in the ICU. Ventilator-associated pneumonia and hospital-acquired pneumonia can produce fever along with worsening gas exchange, increasing ventilatory requirements, purulent secretions, and evolving radiographic infiltrates, though these findings may overlap with non-infectious pulmonary conditions. Sinusitis, particularly in patients with nasogastric tubes, nasotracheal intubation, or prolonged supine positioning, can also be a source of fever and may require dedicated evaluation when other sources are not evident. Intra-abdominal infections are similarly prominent, especially in postoperative patients, those with recent gastrointestinal perforation, pancreatitis, ischemic bowel, or biliary pathology. Nosocomial diarrhea may represent infectious colitis, including infections that emerge after antibiotic exposure and prolonged hospitalization. Acalculous cholecystitis, a condition more frequently encountered in critically ill patients than in ambulatory populations, can present with fever and systemic inflammatory response, often with minimal localizing signs, and may require imaging for detection. Likewise, ischemic bowel and pancreatitis can generate fever as part of severe inflammatory cascades, and they may coexist with secondary infection or bacterial translocation, complicating the clinical picture. Surgical site infections must also be considered when fever occurs following operative interventions, even if external signs are minimal, because deep infections may evolve beneath the surface and manifest primarily through systemic signs such as fever, leukocytosis, and hemodynamic instability [7].

Cardiovascular and intravascular infections provide another major category. Infective endocarditis may be suspected in patients with persistent bacteremia, cardiac devices, prior valvular disease, embolic phenomena, or new murmurs, though these features can be masked or difficult to evaluate in the ICU. Catheter-related bloodstream infection remains a central ICU-specific concern because vascular access is ubiquitous, often multilumen, and frequently manipulated. Fever may be the only early manifestation, but progression can be swift, particularly if infection is complicated by septic thrombophlebitis or metastatic seeding. Renal and urinary infections such as pyelonephritis can also cause fever, though symptom localization is limited in sedated patients; catheter-associated infection is particularly relevant, and bacteremia may be the presenting clue.

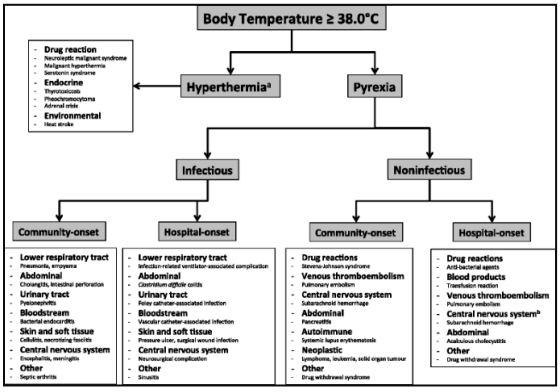

Fig. 1: Fever in ICU.

Skin, soft tissue, bone, and joint infections—including cellulitis, abscesses, osteomyelitis, septic arthritis, and infected decubitus ulcers—are important sources of fever, especially among immobilized patients, those with peripheral vascular disease or diabetes, and patients with prolonged ICU stays where tissue pressure injury can evolve into infected ulcers. These infections may be clinically occult beneath dressings or in less visible anatomic regions unless systematically examined. Non-infectious etiologies of fever are diverse and, in many cases, reflect inflammation, tissue necrosis, thromboembolic disease, endocrinologic crises, autoimmune activation, or drug-related reactions. Central nervous system processes such as cerebral infarction, intracerebral hemorrhage, or subarachnoid hemorrhage can trigger fever via neurogenic mechanisms, including hypothalamic dysregulation and cytokine-mediated inflammation. In such situations, fever may occur without identifiable infection and may correlate with neurologic injury severity. In the respiratory system, fever can accompany acute respiratory distress syndrome, atelectasis, pulmonary embolism, or chemical pneumonitis, each of which may produce systemic inflammatory responses. Distinguishing these from pneumonia can be challenging because both categories may present with hypoxemia and radiographic abnormalities; thus, careful integration of microbiologic data, imaging patterns, temporal course, and response to supportive measures is essential [7].

Within the abdomen, non-infectious sources include ischemic bowel and gastrointestinal bleeding, both capable of eliciting fever through inflammatory mediator release, tissue injury, and transfusion requirements. Acute pancreatitis can generate fever in the absence of infection, particularly early in its course, though secondary infection may develop later and should be suspected with clinical deterioration or persistent systemic inflammation. Cardiovascular non-infectious causes include myocardial infarction, pericarditis, deep vein thrombosis, and thrombophlebitis; these conditions can manifest with fever due to inflammation and tissue injury, and they

carry high clinical significance because delayed recognition can worsen outcomes. In addition, rheumatologic and autoimmune disorders such as systemic lupus erythematosus can flare during critical illness or be unmasked during hospitalization, producing fever and multisystem manifestations that can mimic sepsis. Endocrine emergencies, including adrenal insufficiency, thyroid storm, and pheochromocytoma, may also present with fever and hemodynamic instability; these entities are particularly important to consider when fever is accompanied by disproportionate tachycardia, refractory hypotension, altered mental status, or metabolic derangements that do not align with infectious trajectories. A substantial portion of non-infectious ICU fever is iatrogenic or treatment-associated. Drug fever is a classic example, often presented as persistent or intermittent fever without a clear source, sometimes accompanied by eosinophilia, rash, or mild hepatic abnormalities, though these features are not consistently present. Withdrawal states from alcohol or sedative agents can also produce hyperthermia and autonomic instability. Postoperative fever is another frequent phenomenon; while early postoperative fever may be inflammatory and self-limited, it can also herald surgical site infection, pneumonia, catheter-related infection, or thromboembolic events, necessitating judicious evaluation guided by timing and associated clinical features. Other important treatment-related causes include transfusion reactions, contrast agent reactions, and fat embolism syndromes, each capable of precipitating fever as part of systemic inflammatory responses. Malignancy-associated fever, though less common in the ICU, can appear in patients with hematologic or metastatic disease and may be difficult to separate from infection, especially when immunosuppression and chemotherapy have altered baseline inflammatory markers. Severe cutaneous adverse reactions such as Stevens–Johnson syndrome also present with fever and systemic symptoms, demanding prompt recognition given their high morbidity [7].

Certain fever etiologies are particularly characteristic of, and in some cases largely unique to, the ICU environment because they are strongly linked to critical care devices, prolonged immobility, and healthcare-associated microbial exposure. These include ventilator-associated pneumonia, catheter-related bloodstream infection, catheter-associated urinary tract infection, Clostridoides difficile colitis, pressure ulcer–related infection, and surgical wound–related infection. These syndromes represent a practical "ICU-specific" subset because their incidence is heavily influenced by device utilization, antimicrobial exposure, length of stay, and adherence to infection prevention measures. Recognizing this cluster is clinically useful: when fever develops in an ICU patient, careful reassessment of device necessity, insertion sites, dressing integrity, ventilator parameters, bowel patterns, and skin pressure points can reveal a likely source even before definitive microbiologic confirmation. At the same time, clinicians must remain cautious not to overdiagnose these conditions based solely on fever, particularly when the broader clinical picture suggests a non-infectious inflammatory process or an alternative acute complication. Overall, the etiologic evaluation of fever in intensive care demands a comprehensive and system-oriented approach that acknowledges infections as the most common cause while deliberately maintaining diagnostic openness to non-infectious processes. The high prevalence of sepsis among febrile ICU patients[7] appropriately elevates the priority of infection assessment, yet the heterogeneity of alternative causes requires clinicians to interpret fever within the patient's trajectory, exposures, organ dysfunction patterns, and treatment context. This balanced perspective is essential to ensure timely antimicrobial therapy when indicated, avoid unnecessary antibiotic use when infection is unlikely, and prevent missed diagnoses of non-infectious conditions that can be equally lethal if not promptly identified and managed [7].

Epidemiology

Fever is a highly prevalent clinical finding in intensive care units, yet its reported incidence varies widely across studies, reflecting differences in patient populations, ICU subtypes, and the operational definitions of fever applied. Available data suggest that between 26% and 88% of critically ill patients experience at least one episode of fever during their ICU stay, underscoring the frequency with which clinicians must interpret and manage temperature elevations in this setting.[8][7] This broad range highlights the heterogeneity of intensive care practice, as medical, surgical, trauma, and mixed ICUs differ substantially in baseline disease burden, exposure to invasive interventions, and risk of healthcare-associated infection. Furthermore, variation in temperature measurement methods and fever thresholds contributes meaningfully to discrepancies in reported incidence, complicating direct comparison across studies. Large observational investigations have provided valuable insight into the epidemiology of fever in critically ill populations. In a comprehensive study conducted by Laupland and colleagues, the incidence of fever in combined medical and surgical ICUs was reported to be approximately 44%, while high-grade fever occurred in about 8% of patients.[4] These findings emphasize that although fever is common in the ICU, extreme temperature elevations are comparatively infrequent. The distinction between low-grade and high-grade fever is epidemiologically and clinically relevant, as higher temperatures may carry different prognostic implications and may more strongly prompt diagnostic and therapeutic interventions. In contrast, Barie and co-investigators reported a lower incidence of fever, approximately 26%, among patients in a

surgical ICU.[9] This difference may reflect variations in perioperative management, the timing of temperature measurement relative to surgical stress, or differences in patient selection, reinforcing the importance of contextual interpretation when applying epidemiologic data to individual clinical settings [9].

Beyond overall incidence, epidemiologic studies have examined the relative contributions of infectious and non-infectious etiologies to febrile episodes in the ICU. Notably, several investigations have reported a comparable frequency of infectious and non-infectious causes of fever among critically ill patients.[10] This observation challenges the common assumption that fever in the ICU is synonymous with infection and underscores the necessity of maintaining diagnostic breadth when evaluating temperature elevation. From an epidemiologic perspective, the coexistence of these etiologic categories further complicates surveillance and benchmarking efforts, as identical clinical manifestations may arise from fundamentally different underlying processes with distinct management implications. The relationship between fever severity and patient outcomes has also been explored in large-scale epidemiologic studies. An observational analysis involving 24,204 adult ICU admissions demonstrated that fever reaching or exceeding 39.5°C (103°F) was associated with significantly higher mortality compared with temperatures below this threshold, with mortality rates of 20% versus 12%, respectively.[4] This finding suggests that high-grade fever may serve as a marker of severe physiologic stress, advanced disease, or dysregulated inflammatory response in critically ill patients. Importantly, this association does not necessarily imply causation, as fever may reflect the intensity of the underlying illness rather than acting as an independent driver of mortality. Nonetheless, the epidemiologic signal linking extreme temperature elevation with adverse outcomes reinforces the clinical relevance of fever stratification rather than treating all febrile episodes as equivalent. In addition to mortality, fever has been associated with increased healthcare resource utilization. Epidemiologic data indicate that febrile ICU patients tend to experience longer lengths of stay and incur higher costs of care, likely as a result of extended monitoring, additional diagnostic testing, and prolonged or escalated therapeutic interventions.[4] These associations have implications not only for individual patient outcomes but also for healthcare systems, particularly in resource-constrained environments where ICU capacity and costs are major considerations. From a population-level perspective, the burden of fever in the ICU therefore extends beyond clinical morbidity to encompass economic and operational consequences [6].

Certain patient subgroups appear to be particularly vulnerable to the detrimental effects of fever. Epidemiologic studies have suggested that fever may be associated with poorer outcomes in patients with acute pancreatitis, traumatic head injury, and subarachnoid hemorrhage.[11] In these conditions, elevated temperature may exacerbate underlying pathophysiology by increasing metabolic demand, worsening cerebral edema, or intensifying inflammatory cascades, thereby contributing to secondary injury. Although the epidemiologic evidence does not uniformly establish fever as a causal factor, the consistent association with adverse outcomes in these populations has informed more aggressive temperature management strategies in selected clinical contexts. Taken together, the epidemiology of fever in the ICU illustrates a common but complex phenomenon characterized by substantial variability in incidence, etiology, and outcome associations. Fever affects a large proportion of critically ill patients, with incidence influenced by ICU type, patient characteristics, and definitional criteria.[8][7][9] While both infectious and non-infectious causes contribute meaningfully to febrile episodes,[10] higher levels of fever appear epidemiologically linked to increased mortality, longer ICU stays, and greater healthcare costs.[4] These patterns highlight the importance of nuanced epidemiologic understanding to inform clinical decision-making, resource allocation, and the development of evidence-based protocols for the evaluation and management of fever in critically ill populations.[11]

Pathophysiology

Fever represents a highly regulated physiologic response that arises from complex interactions between the immune system and the central thermoregulatory mechanisms of the body. In critically ill patients, this response is most commonly initiated by exogenous stimuli, such as microbial components, toxins, or tissue injury, which activate innate immune cells including monocytes, macrophages, and other circulating white blood cells. Upon activation, these cells release a cascade of proinflammatory cytokines, most notably interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α).[12][13] These cytokines serve as endogenous pyrogens and constitute the primary molecular signals responsible for initiating the febrile response. Their systemic release reflects both localized inflammatory processes and broader immune activation, a feature that is particularly prominent in critical illness where inflammatory pathways are frequently amplified or dysregulated. The central nervous system plays a pivotal role in translating these peripheral inflammatory signals into an elevation of core body temperature. Proinflammatory cytokines exert their thermogenic effects by interacting with specific receptors located

within the organum vasculosum of the lamina terminalis, a specialized circumventricular structure that lacks a fully developed blood–brain barrier. This anatomic feature allows circulating cytokines to access and influence central neural pathways that would otherwise be shielded from peripheral immune mediators. Activation of cytokine receptors in this region triggers the induction of cyclooxygenase enzymes and the subsequent synthesis of prostaglandins, particularly prostaglandin E2 (PGE2). The production of prostaglandins represents a critical intermediary step in the febrile cascade, serving as the direct link between immune signaling and hypothalamic thermoregulation.[14][15] Once synthesized, PGE2 acts on specific receptors within the hypothalamus to increase intracellular cyclic adenosine monophosphate (cAMP) levels. This biochemical signaling pathway ultimately leads to a resetting of the hypothalamic thermoregulatory set point to a higher level, which the body then perceives as normothermia. In response, physiologic mechanisms aimed at conserving and generating heat are activated, including peripheral vasoconstriction, shivering, increased metabolic rate, and behavioral adaptations where possible. The coordinated activation of these responses results in a rise in core body temperature, manifesting clinically as fever. Importantly, this process is not a passive consequence of heat accumulation but rather an active, centrally mediated adjustment of temperature regulation designed to support host defense mechanisms.

Within the ICU context, the febrile response may be further modulated by factors such as organ dysfunction, pharmacologic agents, sedation, and supportive technologies, all of which can influence cytokine production, prostaglandin synthesis, or hypothalamic responsiveness. Additionally, systemic inflammatory response syndrome and sepsis are characterized by exaggerated cytokine release, which may intensify or prolong fever, whereas in advanced stages of critical illness immune exhaustion may blunt the febrile response altogether. These variations underscore the dynamic and context-dependent nature of fever pathophysiology in critically ill patients. An important and ongoing discussion in the medical literature concerns the pathophysiology of fever in neutropenic patients, particularly those with neutropenic sepsis. There is a prevailing perception that the mechanisms underlying fever in neutropenic individuals differ fundamentally from those in non-neutropenic patients. This view is based on the altered immune landscape in neutropenia, where reduced neutrophil counts and impaired inflammatory signaling may modify cytokine release patterns and downstream responses. Despite these differences, fever in neutropenic patients remains a critical clinical indicator of potential infection, even if the magnitude or accompanying inflammatory features are attenuated. Understanding these pathophysiologic distinctions is essential for interpreting fever appropriately across diverse ICU populations and for tailoring diagnostic and therapeutic strategies to the underlying immune status of the patient.[12][13][14][15]

History and Physical

The evaluation of fever in the intensive care unit must begin with a meticulous clinical assessment grounded in a comprehensive history and a thorough physical examination. Despite the availability of advanced diagnostic technologies in modern ICUs, careful bedside evaluation remains indispensable, as it frequently provides the earliest and most reliable clues to the underlying etiology of fever. In critically ill patients, fever may arise from a wide spectrum of infectious and non-infectious causes, and while both categories must be systematically considered, infectious etiologies carry particular urgency because their identification often necessitates immediate changes in antimicrobial therapy, source control strategies, and overall management plans. Consequently, the clinician's approach should be structured, hypothesis-driven, and sensitive to the unique constraints of the ICU environment, where patient communication may be limited and classic clinical signs may be muted or absent. A detailed history should be obtained to the fullest extent possible, incorporating information from the patient, family members, nursing staff, medical records, and prior hospitalization data. Key historical elements include the timing of fever onset relative to ICU admission or recent interventions, prior or ongoing infections, antimicrobial exposure, recent surgical procedures, use of invasive devices, transfusions, and changes in medications. Equally important is an understanding of the patient's underlying comorbidities, immune status, and recent travel or exposure history, as these factors may narrow or expand the differential diagnosis. In critically ill patients, fever may represent the progression of a pre-existing illness or the emergence of a new complication related to ICU care, and distinguishing between these possibilities requires careful temporal correlation and clinical judgment [12][13].

The physical examination should be comprehensive and deliberately systematic, even when the patient is sedated or mechanically ventilated. Particular attention must be paid to potential portals of entry for infection. Vascular access sites should be carefully inspected and palpated for erythema, tenderness, discharge, or induration, as intravascular catheters are among the most common sources of ICU-acquired infection. Urinary catheters, drain sites, and surgical incision sites must likewise be examined for signs of local inflammation or purulence, recognizing that deep or organ-space infections may present minimal superficial findings. Cardiovascular examination is essential, and heart sounds should be auscultated carefully to detect new murmurs or changes that might suggest infective endocarditis, particularly in

patients with persistent bacteremia, indwelling lines, or prior valvular disease. Respiratory evaluation is another critical component of the physical examination in febrile ICU patients. Tracheal secretions should be assessed for changes in color, odor, viscosity, and volume, as purulent or malodorous secretions may suggest lower respiratory tract infection. Although these findings are not diagnostic in isolation, they can support suspicion for ventilator-associated pneumonia when interpreted alongside radiographic and laboratory data. Examination of the skin and soft tissues should be performed routinely and meticulously, as cellulitis, furunculosis, paronychia, and infected pressure injuries are common yet sometimes overlooked sources of fever in immobilized patients. Subtle or clinically silent foci of infection, including sinusitis, decubitus ulcers, dental or tonsillar infections, perineal wounds, and deep-seated abscesses, require a particularly high index of suspicion, as they may not produce overt local symptoms but can generate significant systemic inflammatory responses. Medication review is a mandatory component of the evaluation, as drug-induced fever remains an important non-infectious cause of temperature elevation in the ICU. Drug fever is typically a diagnosis of exclusion and should be considered when fever persists despite appropriate antimicrobial therapy and when no infectious source can be identified. A careful review of recently initiated or escalated medications, including antibiotics, anticonvulsants, and other commonly implicated agents, is therefore essential. Similarly, alcohol or sedative withdrawal should be considered in appropriate clinical contexts, as these conditions may present with hyperthermia and autonomic instability [12][13].

Special consideration must be given to immunocompromised and neutropenic patients, in whom the classical manifestations of infection and inflammation are often blunted. In these populations, fever may be the sole indicator of a serious underlying infection, and overt localizing signs may be absent. As a result, clinicians must rely on subtle clinical cues and maintain a heightened level of suspicion. Skin findings such as ulcers, nodules, vesicles, pilonidal sinuses, and characteristic lesions including erythema multiforme and ecthyma gangrenosum may serve as critical diagnostic clues and should be actively sought, particularly in neutropenic or immunosuppressed patients. Perianal infections, in particular, are frequently missed in neutropenic individuals due to minimal pain or external inflammation, yet they can rapidly progress to life-threatening sepsis if not recognized promptly. Accurate measurement of body temperature is a fundamental aspect of fever assessment in the ICU. Core body temperature measurement is preferred, as peripheral measurements may be unreliable in critically ill patients with altered perfusion or thermoregulation. The thermistor of a pulmonary artery catheter is considered the gold standard for core temperature measurement; however, its invasive nature limits routine use. Consequently, less invasive methods such as nasopharyngeal, esophageal, and bladder thermistors are commonly employed, followed by rectal and tympanic membrane measurements.[16] In contrast, axillary, oral, and forehead temperature measurements lack sufficient accuracy in the ICU setting and should be avoided. Some experts suggest that the magnitude of fever may provide indirect clues to its etiology.[17][18][19] Based on this perspective, temperatures between 38.3°C and 38.8°C may be associated with both infectious and non-infectious causes, encompassing a broad differential diagnosis. Fevers exceeding 38.9°C (102°F) but below 41°C are more often infectious in origin, whereas extreme hyperthermia at or above 41.1°C (105.8°F) is generally considered non-infectious. While such categorizations should not replace comprehensive evaluation, they may aid clinical reasoning when integrated with history, examination, and ancillary investigations.[16][17][18][19]

Evaluation

The diagnostic evaluation of fever in the intensive care unit must be systematic, timely, and proportionate to the patient's physiologic instability, baseline risk factors, and the likelihood of an infectious source. Because fever in critical illness may represent sepsis, noninfectious inflammation, iatrogenic complications, or evolving organ injury, a structured approach that integrates biochemical assessment, microbiologic sampling, biomarker interpretation, imaging, and targeted invasive procedures is essential. The central principle is to identify life-threatening etiologies early, obtain adequate cultures before antimicrobial escalation whenever feasible, and avoid indiscriminate testing that may yield misleading results or expose the patient to unnecessary risk. From a biochemical standpoint, serum lactate measurement occupies a central role in the early evaluation of suspected sepsis and septic shock. Lactate elevation is commonly observed in states of impaired tissue oxygen utilization, circulatory dysfunction, and high metabolic stress. A lactate level exceeding 2 mmol/L is incorporated into the 2016 Third International Consensus Definitions for Sepsis and Septic Shock as a component of septic shock criteria, reflecting its prognostic value and association with more severe disease.[20] The pathophysiologic basis for lactate elevation includes increased production due to anaerobic metabolism in hypoperfused tissues and reduced clearance, particularly in the context of hepatic dysfunction. Serial lactate measurement can therefore support both diagnostic reasoning and assessment of resuscitation response, although

clinicians must interpret lactate cautiously, recognizing that elevations may occur in noninfectious conditions such as seizures, severe adrenergic stress, or hepatic failure [20].

A complete blood count and renal and hepatic function panels are foundational investigations in febrile ICU patients. Leukocytosis or leukopenia may provide supportive evidence of systemic inflammation or marrow suppression, while thrombocytopenia may signal evolving sepsis, disseminated intravascular coagulation, drug effects, or underlying hematologic disease. Kidney and liver function tests are essential not only for identifying organ dysfunction related to the febrile illness but also for guiding antibiotic selection, dosing, and monitoring for drug toxicity. When abdominal pathology is clinically suspected, particularly in patients with abdominal pain or unexplained systemic inflammatory response, serum amylase and lipase are helpful to evaluate for pancreatitis, a condition that can produce fever from sterile inflammation or complicated infection. In specific clinical contexts such as suspected transfusion reactions, the evaluation becomes more specialized and may require a direct antiglobulin test, measurement of haptoglobin and free plasma hemoglobin, and repeat blood grouping and cross-matching, because hemolytic transfusion reactions can present with fever and hemodynamic instability and may have immediate management implications. Endocrine etiologies should not be overlooked, especially when fever is accompanied by disproportionate tachycardia, refractory shock, altered mental status, or other suggestive features. In suspected thyroid storm, assessment of thyroid function tests is required to support diagnosis and initiate time-sensitive therapy. Similarly, adrenal insufficiency must be considered in vasopressor-refractory hypotension or unexplained fever, and evaluation may involve measurement of free cortisol levels or an ACTH stimulation test to confirm impaired adrenal reserve. These assessments are particularly important because endocrine crises can mimic septic shock and may coexist with infection, necessitating parallel evaluation rather than sequential exclusion [20].

Microbiologic investigation remains the cornerstone of evaluating potentially infectious fever in the ICU. Fresh cultures should be obtained before initiating new antibiotics or modifying ongoing antimicrobial regimens whenever clinically possible, because prior antibiotic exposure reduces culture yield and complicates pathogen identification. Blood cultures are recommended in all febrile ICU patients, given the frequency and severity of bacteremia in critical illness and the potential for bloodstream infection to be the primary source or a manifestation of infection elsewhere. Additional cultures should be guided by suspected foci of infection. Respiratory tract sampling, such as tracheal secretions or bronchoalveolar lavage (BAL), is appropriate when pneumonia is suspected; urine cultures should be obtained when catheter-associated infection or pyelonephritis is considered; and cerebrospinal fluid culture is indicated in suspected meningitis, provided there are no contraindications to lumbar puncture or neuroimaging requirements. This targeted sampling strategy improves diagnostic yield and reduces noise introduced by cultures that are unlikely to be clinically meaningful. The role of inflammatory biomarkers requires nuanced interpretation. C-reactive protein (CRP) is an acute-phase reactant that rises in response to inflammatory stimuli and has long been used as a supportive biomarker in suspected sepsis. However, CRP is nonspecific and increases in a wide range of inflammatory states, including trauma, postoperative inflammation, autoimmune disease, and malignancy, which limits its discriminative utility in the ICU where such conditions are common. Procalcitonin has gained prominence as an adjunct biomarker, often providing more informative correlation with bacterial infection burden and severity of illness compared with CRP. Procalcitonin-guided strategies have been incorporated into antibiotic stewardship efforts, with evidence suggesting utility in reducing unnecessary antibiotic exposure and supporting earlier discontinuation in appropriate settings.[21][22] Nonetheless, available evidence does not support using procalcitonin alone to initiate antibiotic therapy, particularly given the high stakes of delayed treatment in severe sepsis. Clinicians must also recognize that procalcitonin can be elevated in noninfectious etiologies such as major trauma, extensive surgery, multiorgan failure even without infection, and myocardial infarction, which can lead to false-positive inference of bacterial sepsis if used uncritically. Importantly, markedly elevated procalcitonin levels may correlate with worse prognosis and higher mortality in septic patients, indicating that it may serve as a risk stratification marker rather than a standalone diagnostic tool.[23]

Imaging studies are integral to source identification and to distinguishing infectious from noninfectious pathology. Chest radiography is typically the first-line modality for evaluating respiratory causes of fever and can assist in differentiating pneumonia from tracheobronchitis. However, its sensitivity is limited in certain populations, especially neutropenic patients, in whom radiographic infiltrates may be absent despite significant pulmonary pathology. In one reported context, approximately half of neutropenic patients with bone marrow suppression and stem cell transplantation had normal chest radiographs despite abnormalities detected on high-resolution computed tomography (HRCT) of the thorax.[24] This observation supports early escalation to CT-based imaging when clinical suspicion remains high despite an unrevealing chest X-ray, particularly in immunocompromised patients. Bedside ultrasound

provides an attractive, low-risk, repeatable adjunct to fever evaluation. Lung ultrasound has demonstrated high sensitivity for detecting consolidations and pleural abnormalities, though specificity can be lower due to overlap between infectious consolidation and noninfectious inflammatory changes. Abdominal and pelvic ultrasound can identify hepatobiliary sources, ascites, or gross collections, yet it has limited capability for detecting retroperitoneal pathology, and intraluminal gas can significantly obscure acoustic windows. When thromboembolic disease is suspected, compression ultrasonography and venous Doppler studies are appropriate to evaluate for deep vein thrombosis, a recognized noninfectious cause of fever. In selected cases, arterial Doppler studies may be required to detect early or subtle limb ischemia, which can produce fever through tissue injury and inflammatory mediator release. Computed tomography frequently becomes the definitive imaging modality when initial evaluation is inconclusive or when deep-seated infection is suspected. CT of the thorax may detect pleural empyema not visible on plain radiography, facilitating prompt drainage and source control. Contrast-enhanced abdominal CT is often employed when intra-abdominal infection is suspected but not identified clinically or sonographically, enabling detection of conditions such as acalculous cholecystitis, liver abscess, or postoperative collections. When mesenteric ischemia is a concern, CT angiography is required, given that early diagnosis significantly influences outcomes. Evaluation for sinusitis warrants particular attention in ICU patients, especially those who are neutropenic or those with unexplained fever and no clear source, because sinus infections can be clinically silent in sedated or ventilated patients. This assessment often requires a high index of suspicion and is typically confirmed through CT imaging of the paranasal sinuses. Whole-body positron emission tomography is rarely required in the ICU, but it may occasionally be considered in persistent fever of unknown origin when conventional imaging and cultures fail to reveal a source, and when identifying an occult focus would meaningfully change management [21].

Endoscopic and invasive diagnostic interventions are reserved for selected cases where noninvasive evaluation is insufficient or where direct visualization and sampling may significantly improve diagnostic accuracy. Fibreoptic bronchoscopy with BAL can be particularly valuable in diagnosing atypical pulmonary infections, opportunistic pathogens, or noninfectious conditions that mimic pneumonia. In parallel, gastrointestinal endoscopy may be used when a gastrointestinal source of fever is suspected, whether infectious or inflammatory. Colonoscopy is rarely necessary but may be considered to confirm pseudomembranous colitis in strongly suspected Clostridioides difficile infection when standard tests are negative, given the potential severity and infection control implications of missed diagnosis. Microbiologic best practices emphasize proper technique and timing, particularly for blood cultures. Blood cultures should be drawn from two separate sites, using both aerobic and anaerobic bottles, and should ideally be obtained before antimicrobial therapy begins. In patients with central venous access, cultures should also be drawn from the catheter to aid in diagnosing catheter-related bloodstream infection and to permit differential time-to-positivity interpretation. When fungal infection is suspected, additional inoculation into fungal culture bottles is recommended to improve diagnostic yield, particularly in patients with prolonged ICU stays, total parenteral nutrition, broad-spectrum antibiotic exposure, or immunosuppression. Finally, respiratory tract sampling should be performed when clinically appropriate; endotracheal aspirate or sputum Gram stain and culture can provide early microbiologic guidance, although results must be interpreted alongside clinical findings and imaging to distinguish colonization from true infection. In summary, evaluation of fever in the ICU requires a deliberate integration of laboratory biochemistry, microbiologic sampling, biomarker interpretation, imaging selection, and targeted invasive diagnostics. Lactate and organ function tests provide essential physiologic and prognostic information,[20] while cultures remain foundational to pathogen identification and antimicrobial optimization. Biomarkers such as CRP and procalcitonin can support clinical reasoning and stewardship when interpreted within context rather than used as definitive tests.[21][22][23] Imaging and endoscopic interventions should be chosen according to suspected source, patient risk factors, and the limitations of each modality, including reduced radiographic sensitivity in neutropenic patients.[24] This structured approach improves the likelihood of timely diagnosis, appropriate therapy, and avoidance of unnecessary interventions in the complex and heterogeneous population of critically ill febrile patients.

Treatment / Management

Management of fever in the intensive care unit is inseparable from management of the underlying process that has generated the temperature elevation. While fever is a salient clinical sign, it is not itself a diagnosis; therefore, treatment strategies must prioritize early recognition of infection and sepsis, rapid initiation of appropriate antimicrobial therapy when indicated, prompt source control, and judicious consideration of antipyretic interventions. The ICU context further demands careful balancing of risks and benefits because interventions undertaken to treat fever—particularly broad-spectrum antibiotics and aggressive temperature reduction—can carry meaningful downstream consequences, including antimicrobial resistance,

drug toxicity, hemodynamic compromise, and masking of clinically informative trends. Empirical antibiotic therapy remains the cornerstone of management when infection is suspected, particularly when the patient meets criteria for sepsis or demonstrates clinical deterioration suggestive of evolving septic physiology. In such cases, antimicrobial therapy should be initiated only after appropriate microbiologic cultures have been obtained, provided that culture acquisition does not cause clinically unacceptable delays. The importance of timely antibiotic delivery is greatest in septic shock, where mortality rises with delays in effective therapy, and where early empiric coverage may be lifesaving. Antibiotic selection in critically ill febrile patients must be individualized, integrating the likely pathogen profile, the suspected anatomic source, local epidemiology as reflected in institutional antibiograms, and patient-specific risk factors for multidrug-resistant organisms. Such risk factors include prolonged hospitalization, prior broad-spectrum antibiotic exposure, immunosuppression, indwelling devices, repeated invasive procedures, and colonization history. Furthermore, dosing strategies must reflect the altered pharmacokinetics of critical illness. Changes in volume of distribution, augmented renal clearance, hepatic dysfunction, and extracorporeal support can all influence drug concentrations, making it essential that antibiotics be administered at correct doses and intervals for the appropriate duration rather than merely "given." Inadequate dosing risks therapeutic failure, while excessive dosing increases toxicity without improving outcomes [24].

Antibiotic stewardship principles are particularly relevant in ICU fever management because the unit environment is a key driver of global antimicrobial resistance. De-escalation represents a structured approach to minimizing unnecessary antimicrobial exposure while maintaining clinical safety. In practice, de-escalation may include narrowing the antimicrobial spectrum based on culture and susceptibility data, transitioning from intravenous to oral therapy when enteral absorption is reliable and the clinical state permits, and discontinuing antibiotics once an adequate therapeutic course has been completed or when infection is no longer supported by clinical and microbiologic evidence. This approach aims to preserve antibiotic effectiveness at a population level while also reducing individual risks such as Clostridioides difficile infection, drug-related adverse effects, and selection for resistant flora. Importantly, de-escalation should not be misconstrued as undertreatment; rather, it is a refinement of therapy as diagnostic uncertainty resolves. Alongside antimicrobial therapy, source control is an equally critical pillar in the treatment of infection-related fever and sepsis. Antibiotics alone may be insufficient when an infected focus persists, particularly when bacterial burden remains high or when organisms are protected within collections or biofilms. The source must therefore be actively sought and addressed without delay. Source control encompasses a range of interventions, including removal or replacement of intravascular catheters when catheter-related bloodstream infection is suspected, discontinuation of urinary catheters when feasible, and drainage of purulent collections such as empyema or abscesses. In certain circumstances, surgical intervention may be required for definitive control of intra-abdominal infection, necrotizing soft tissue infection, or infected prosthetic material. The timing of source control is often decisive; delays can permit ongoing microbial replication, continued toxin production, and sustained inflammatory activation, thereby perpetuating hemodynamic instability and organ dysfunction even in the presence of appropriate antimicrobial therapy [25][26].

The management of fever also frequently raises the question of antipyretic use and temperature reduction strategies. Antipyretics act primarily by lowering the hypothalamic set point through inhibition of prostaglandin-mediated signaling, thereby reducing body temperature. The decision to treat fever pharmacologically is complex because fever may be biologically advantageous in infection. Febrile temperatures can inhibit bacterial replication and may enhance host immune responses through increased cytokine activity and activation of immune effector cells such as neutrophils, macrophages, and T lymphocytes.[25][26] At the same time, fever is not physiologically cost-free. Elevated temperature increases metabolic rate and oxygen consumption, which can be detrimental in patients with limited cardiopulmonary reserve or compromised oxygen delivery.[27] Additionally, reducing temperature has been associated with lowered lactate levels in septic patients, suggesting potential hemodynamic or metabolic benefits in certain contexts.[28] Whether the energetic cost of pyrexia translates into worse clinical outcomes across heterogeneous ICU populations remains uncertain, and the literature has not yielded uniform conclusions. However, one domain in which the adverse impact of fever is strongly supported is acute neurologic injury, where hyperthermia has been consistently linked to higher mortality and poorer neurologic outcomes.[29][30][31][32] This distinction is clinically important because it implies that temperature control policies should be tailored to patient phenotype rather than universally applied. Evidence from controlled studies has not established clear outcome benefits for aggressive fever suppression in ICU patients without acute central nervous system pathology. The REACTOR trial, which randomized 184 febrile ICU patients who did not have acute CNS disease, compared systematic active temperature management with ordinary temperature management and found no difference in

ICU-free days or 90-day survival.[33] These findings suggest that routine, protocolized fever suppression may not improve major clinical outcomes in broadly selected ICU populations. More broadly, studies evaluating aggressive temperature control using external cooling devices or acetaminophen have been criticized for methodological limitations, and available data remain insufficient to support definitive conclusions.[34][35] Accordingly, contemporary practice in many ICUs favors individualized antipyretic use, guided by fever magnitude, hemodynamic tolerance, patient discomfort when assessable, and the presence of conditions in which fever is known to be harmful.

The clinical question is therefore not simply whether fever should be treated, but rather in whom and under what circumstances fever reduction is likely to be beneficial. Extremely high fever appears to represent a distinct risk category. A temperature above 40°C has been associated with increased mortality in patients without evidence of infection and is generally regarded as an indication for aggressive temperature control.[6] In contrast, moderate fever in the range of 37.5°C to 38.4°C has been associated with decreased mortality in septic patients, suggesting that modest temperature elevation may reflect a protective host response in infection and may not require suppression.[5] A meta-analysis has further reported that antipyretic therapy does not reduce mortality and does not appear to change rates of nosocomial infection acquisition among critically ill patients with sepsis, reinforcing the view that routine antipyresis is not an evidence-based strategy for improving survival in this population [36]. These findings support a selective approach: permissive fever may be reasonable in stable septic patients, whereas high-grade fever or fever in neurologic injury may warrant active intervention. When antipyretic therapy is chosen, acetaminophen is generally preferred over aspirin in the ICU due to a more favorable safety profile, particularly with respect to bleeding risk, platelet inhibition, and gastrointestinal adverse effects. Enteral acetaminophen has excellent bioavailability, and oral or enteral administration is preferred whenever the gastrointestinal route is available and not contraindicated. Intravenous acetaminophen is typically reserved for situations in which enteral administration is not feasible. Importantly, available evidence indicates that hypotension—defined in some studies as a systolic blood pressure of 90 mmHg or less, or a reduction of at least 20% from baseline—may occur more frequently with intravenous acetaminophen than with oral formulations.[37][38] This hemodynamic consideration is especially relevant in critically ill patients who may already be vasodilated, volume-depleted, or dependent on vasopressor support. Therefore, the route of administration should be selected thoughtfully, balancing the need for reliable absorption against the potential for adverse circulatory effects. In sum, treatment and management of fever in the ICU should prioritize early antimicrobial therapy in suspected infection after appropriate cultures are obtained, rapid and definitive source control when infection is identified, and individualized temperature management strategies that account for the potential benefits of fever, its metabolic costs, and the strong evidence of harm in neurologic injury.[25][26][27][28][29][30][31][32] (A1) Current evidence does not convincingly support routine aggressive fever suppression in ICU patients without CNS pathology, as demonstrated by randomized data such as the REACTOR study,[33] and broader analyses remain limited by methodological concerns.[34][35] The most rational approach therefore integrates severity-based decision-making—aggressively controlling extreme hyperthermia when indicated,[6] while avoiding unnecessary antipyresis in moderate septic fever where potential benefit may exist and mortality may even be lower.[5][36[.

Differential Diagnosis

Fever in the intensive care unit is frequently approached as a surrogate for infection, and indeed infectious processes account for a substantial proportion of febrile episodes in critically ill patients. Nevertheless, the diagnostic framework must remain deliberately broad. Non-infectious etiologies are common in the ICU because critical illness itself is an inflammatory state, and because patients are exposed to numerous interventions and medications that can precipitate temperature elevation through mechanisms unrelated to microbial invasion. Failure to recognize non-infectious causes can lead to indiscriminate escalation of antimicrobials, exposing patients to avoidable adverse drug effects, Clostridioides difficile infection, drug–drug interactions, and selection pressure that accelerates the emergence of multidrug resistance. Accordingly, differential diagnosis in the ICU requires a disciplined, syndromic approach that integrates the timing of fever onset, recent procedures and device exposures, the pattern of organ dysfunction, microbiologic data, and imaging findings, while continuously reassessing the probability of infection as new information emerges. Postoperative fever represents one of the most common and often misunderstood febrile syndromes encountered in the ICU. Temperature elevation within the first 48 hours following surgery is frequently observed and is usually noninfectious, reflecting the physiologic inflammatory response to tissue injury, anesthetic exposure, and transient cytokine release. In many cases, early postoperative fever is self-limited and does not require extensive evaluation, particularly when the patient is clinically stable and there are no

localizing signs of infection. In contrast, fever that develops later—classically after 72 to 96 hours—more often signals an infectious complication and warrants structured investigation. During this later period, surgical wound evaluation becomes essential, including inspection for erythema, warmth, tenderness, discharge, or dehiscence, and consideration of deeper organ-space infection when systemic signs are disproportionate to superficial findings. Beyond surgical site infection, additional postoperative considerations include atelectasis, urinary tract infection, deep vein thrombosis, suppurative phlebitis, and pulmonary embolism. Because critically ill patients may have limited ability to report symptoms and may display blunted physical signs due to sedation or analgesia, postoperative fever assessment should remain methodical, linking the temporal evolution of fever to perioperative events, device placement, transfusions, and mobilization status [36].

Ventilator-associated pneumonia (VAP) is a central ICU-specific infectious diagnosis, defined as pneumonia occurring at least 48 hours after endotracheal intubation. Pneumonia in this context is identified by the presence of new or progressive pulmonary infiltrates combined with evidence that the process is infectious, such as new onset fever, purulent sputum, leukocytosis, and deterioration in oxygenation.[39] Because radiographic abnormalities are common in critically ill ventilated patients for reasons unrelated to infection, clinical suspicion must be supported by appropriate microbiologic sampling from lower respiratory tract secretions and interpreted in light of ventilatory trends and hemodynamic status.[40] Prevention is a major determinant of VAP burden, and ICU programs frequently rely on infection control practices and ventilator “bundles” aimed at reducing aspiration risk, minimizing ventilator days, and standardizing airway management. When VAP is suspected, treatment typically involves intravenous antibiotics initiated empirically in accordance with local antibiogram patterns and the patient’s risk for resistant organisms, followed by refinement to pathogen-specific therapy once culture results become available.[39] This diagnostic and therapeutic pathway underscores a broader ICU principle: VAP management must balance the imperative for early effective therapy against the harms of unnecessary broad-spectrum coverage. Catheter-related bloodstream infection (CRBSI) is another high-priority consideration in the febrile ICU patient and remains a leading cause of nosocomial bacteremia. CRBSI is defined as a bloodstream infection attributable to an intravenous catheter, and a definitive diagnosis is established when the same organism is recovered from at least one percutaneous blood culture and from the catheter tip culture.[41] Clinically, patients may present with fever alone or with systemic signs of sepsis, and local catheter site inflammation may be absent, particularly when infection is intraluminal or related to biofilm. Management typically requires catheter removal when feasible, coupled with systemic antibiotics selected according to suspected pathogens, illness severity, and antimicrobial susceptibility patterns.[41] Given the high frequency of central venous access in critically ill patients, prevention and early recognition are essential components of ICU quality and safety, and persistent fever without an alternative source should prompt renewed scrutiny of intravascular devices [40][41].

Catheter-associated urinary tract infection (CAUTI) is also common in the ICU due to widespread use of indwelling urinary catheters for monitoring output and managing urinary retention. CAUTI refers to a urinary tract infection in a patient who currently has a urinary catheter or who was catheterized within the preceding 48 hours. Proper diagnostic sampling is critical to avoid contamination or misleading results; urine should be obtained directly from the catheter sampling port rather than from the drainage bag. If the catheter has remained in situ for more than two weeks, it should be replaced prior to obtaining a diagnostic specimen, and the sample should be drawn from the newly placed catheter to improve interpretability and reduce biofilm-related confounding.[42] Management typically includes catheter reassessment with removal when possible, targeted antibiotic therapy based on culture results, and evaluation for complications such as pyelonephritis or bacteremia in patients with systemic manifestations. Pressure ulcers occupy a more complex position in the fever differential diagnosis. A pressure ulcer is often discussed as a non-infectious cause of fever in the ICU, yet in practice these lesions frequently become secondarily infected and can serve as a portal for bacteremia and sepsis. Their incidence varies widely across care settings, with published prevalence estimates ranging from 5% to 40%.[43][44][45] This variability reflects differences in patient case-mix, mobility constraints, staffing patterns, preventative protocols, and duration of critical illness. Pressure ulcers are clinically important because they prolong hospitalization, intensify patient suffering, increase mortality risk, and impose substantial economic burden.[43][44][45] In the febrile ICU patient, skin examination should therefore include careful inspection of pressure points and existing ulcers, assessment for surrounding cellulitis or necrosis, and consideration of deeper involvement such as osteomyelitis when ulcers are advanced or chronic.

Acalculous cholecystitis is a particularly relevant diagnosis in the ICU because it often arises in critically ill patients without gallstones and may present with limited localizing signs. It is an inflammatory disease of the gallbladder that occurs due to impaired gallbladder emptying and stasis, and it has been reported to occur in approximately 1.5% of critically ill patients.[46] It is typically

encountered as a complication of severe systemic illness or after major surgery or trauma. Clinically, it may manifest as fever with sepsis, jaundice, and right upper quadrant pain or tenderness, although pain may be difficult to assess in sedated patients. Diagnosis is commonly supported by abdominal ultrasound, with CT imaging employed when sonographic findings are equivocal or when alternative intra-abdominal processes are suspected.[46] In unstable patients, initial management may involve percutaneous gallbladder drainage or endoscopic decompression via ERCP and stent placement, while cholecystectomy remains definitive treatment when the patient's condition allows.[46] Because delayed recognition can lead to gallbladder necrosis or perforation, this entity must remain prominent in the differential diagnosis of unexplained ICU fever. Nosocomial sinusitis is frequently under-recognized in the ICU, yet it can be a clinically meaningful source of persistent fever and may coexist with other respiratory infections. Predisposing factors include nasogastric or nasotracheal tubes, facial fractures, nasal packing, and systemic corticosteroid therapy.[47] Diagnosis is often challenging because ventilated or sedated patients cannot report facial pain, congestion, or headache, and physical examination is limited. Consequently, diagnosis relies heavily on imaging, with CT scanning of the paranasal sinuses providing strong diagnostic utility.[48] Microbiologic confirmation may be achieved through antral puncture or endoscopic sampling for culture, though such procedures require expertise and careful risk assessment. Nosocomial sinusitis is often associated with ventilator-associated pneumonia, potentially reflecting shared risk factors and contiguous microbial colonization.[47] Treatment typically involves removal of precipitating foreign bodies when feasible, use of nasal vasoconstrictors in selected cases, and antibiotic therapy tailored to suspected or confirmed pathogens.

Nosocomial diarrhea is another important contributor to fever in hospitalized and critically ill patients. The most commonly implicated infectious cause of febrile diarrhea in this context is Clostridioides (formerly Clostridium) difficile infection, which typically emerges after antibiotic exposure that disrupts normal colonic flora. Clindamycin is classically associated with increased risk, though many antibiotics can precipitate disease.[49] Diagnostic criteria incorporate clinical evidence of diarrhea—typically increased stool liquidity and frequency—combined with laboratory detection of toxins produced by the organism in stool specimens. Management includes supportive care, discontinuation of inciting antibiotics when possible, and targeted antimicrobial therapy to eradicate C. difficile, such as metronidazole, oral vancomycin, or fidaxomicin.[49] Infection prevention is pivotal; handwashing with soap and water is recommended because alcohol-based hand rubs are ineffective against spores.[49] In ICU patients, the consequences of missed or delayed diagnosis include severe colitis, toxic megacolon, and hemodynamic compromise, making this condition an essential consideration in febrile patients with gastrointestinal symptoms or unexplained leukocytosis. Drug fever is an important noninfectious diagnosis in the ICU and is estimated to account for approximately 3% to 5% of febrile episodes.[50] It remains largely a diagnosis of exclusion, requiring clinicians to rule out infectious and other inflammatory etiologies before attributing fever to medication exposure. The most persuasive clinical clue is the temporal relationship between fever onset and initiation of a drug, as well as fever resolution after discontinuation. Common causative agents include antibiotics—particularly beta-lactams—antiepileptic drugs such as phenytoin, antiarrhythmic agents like quinidine and procainamide, and other medications including diuretics, allopurinol, and heparin.[16] Fever often develops approximately 7 to 10 days after starting the offending drug and typically resolves within 72 hours of drug withdrawal, although this timeline may vary with drug half-life, organ dysfunction, and concomitant inflammatory states.[51] Recognizing drug fever has practical importance because continuing the culprit medication can perpetuate fever, prompt unnecessary antibiotic escalation, and delay identification of the true cause of the patient's clinical trajectory.

Hyperthermia syndromes must be distinguished from fever because they reflect fundamentally different thermoregulatory physiology. Hyperthermia is defined as a core body temperature exceeding 41°C and differs from fever in that the temperature elevation occurs above the hypothalamic set point rather than through set-point resetting. As a result, hyperthermia does not respond predictably to standard antipyretic pharmacotherapy and instead requires immediate nonpharmacologic cooling and targeted treatment of the underlying syndrome. Hyperthermia syndromes include heat stroke, malignant hyperthermia, neuroleptic malignant syndrome, and serotonin syndrome, each with distinct triggers and associated neuromuscular and autonomic findings. Endocrine conditions such as thyrotoxicosis, adrenal crisis, and pheochromocytoma may also cause severe hyperthermia, often accompanied by profound hemodynamic instability, metabolic derangements, and altered mental status. In the ICU, these diagnoses must be considered urgently because delayed recognition can lead to rapid progression to multiorgan failure and death. Evidence from pertinent studies and ongoing trials informs, but does not fully resolve, the question of how aggressively fever should be treated in critically ill patients. The HEAT trial compared acetaminophen with placebo in

patients with fever of at least 38°C and known or suspected infection, demonstrating a moderate reduction in temperature but no difference in mortality at 28 or 90 days, and no difference in ICU-free days.[35] Broader synthesis of the literature has yielded similar conclusions. A meta-analysis of randomized controlled trials reported that more active fever management did not confer a survival benefit in critically ill patients.[52] Another meta-analysis found that while antipyretics reduce temperature in non-neurocritical patients, they do not reduce mortality or improve other key outcomes.[53] Collectively, these data support a nuanced approach in which fever management is tailored to clinical context, particularly recognizing the strong evidence of harm from fever in neurologic injury while acknowledging uncertainty regarding benefit in general ICU populations.

Prognosis:

Prognosis in febrile ICU patients is strongly influenced by both the underlying cause of fever and the patient's baseline physiologic reserve. In acute stroke and other neurologic injuries, fever itself—regardless of etiology—has been associated with worse functional outcomes and longer hospital stays.[32] This relationship likely reflects the deleterious effects of hyperthermia on cerebral metabolism, excitotoxicity, and secondary injury pathways. In contrast, among non-neurological ICU patients, the evidence that fever independently increases mortality remains inconsistent, and outcomes often track more closely with the cause of fever, the severity of associated organ dysfunction, and the timeliness of definitive management. Thus, prognosis should be framed as etiology-dependent, with fever serving in many cases as a marker of the underlying insult rather than a uniform determinant of outcome [32].

Complications:

The complications of fever extend beyond discomfort and include measurable physiologic burdens that can be clinically significant in critical illness. Fever increases cardiac output requirements, elevates oxygen consumption, and increases carbon dioxide production, thereby intensifying ventilatory demand and potentially worsening respiratory failure.[54] In selected populations, fever has more specific adverse consequences. Febrile convulsions occur primarily in children between three months and six years of age and often have a familial predisposition, highlighting that fever-related neurologic events can be consequential even when the fever is otherwise benign. In critically ill adults with traumatic brain injury or cerebrovascular accidents, fever is consistently associated with worsened neurologic outcomes.[55][32] Clinically, a new fever in such patients may coincide with a decline in Glasgow Coma Scale score, prompting urgent evaluation for infection, intracranial complications, or neurogenic fever. Fever also carries important considerations in pregnancy, where maternal hyperthermia has been associated with fetal malformations and spontaneous abortion.[56] Sustained high fever can precipitate rhabdomyolysis and acute kidney injury, sometimes severe enough to require renal replacement therapy, emphasizing that prolonged or extreme hyperthermia can cause direct tissue injury independent of infection. Fever also generates indirect harms: the financial costs of repeated evaluations and treatment, prolonged ICU stays, and—importantly—the tendency for unexplained fever to drive empiric antibiotic overuse, which increases economic burden and promotes multidrug resistance. Because fever in the ICU can be diagnostically challenging and clinically high-stakes, consultations often play a pivotal role. Infectious disease consultation may be particularly valuable when fever persists despite appropriate empiric therapy, when cultures are negative, yet sepsis physiology continues, or when unusual pathogens or complex antimicrobial decisions are involved. Persistent fever of unknown origin, especially when accompanied by non-resolving sepsis or septic shock, often necessitates urgent multidisciplinary collaboration and aggressive diagnostic strategies. Close coordination with radiology can expedite the identification of occult collections, device complications, sinus disease, or ischemic processes, enabling earlier intervention. Depending on the evolving differential diagnosis, pulmonologists may assist with bronchoscopy and complex pneumonia evaluation, rheumatologists may evaluate suspected autoimmune fever syndromes, endocrinologists may assess thyroid or adrenal emergencies, and surgeons may be required for source control of intra-abdominal or soft tissue infection. This consultative approach reflects the reality that ICU fever is rarely confined to one organ system and often demands expertise spanning multiple disciplines [56].

Patient Education:

patient education, while sometimes overlooked in ICU discourse, are important components of comprehensive fever management, especially when the patient lacks decisional capacity and family members act as surrogates. Families or guardians should be counseled regarding the rationale for repeated investigations and monitoring when fever occurs, including why cultures, imaging, and potentially invasive procedures may be necessary to identify life-threatening causes. This need for communication becomes even more pressing when fever emerges de novo during ICU admission without an obvious source, particularly in the presence of sepsis or septic shock features. Transparent discussions about potential complications, anticipated morbidity such as prolonged ICU stay, and the real risk of mortality associated with secondary sepsis can improve understanding, reduce distress, and support shared decision-making consistent with patient values when choices about invasive interventions arise [56].

Enhancing Outcomes:

Enhancing outcomes in febrile ICU patients depends heavily on an interprofessional team approach. Fever can represent a diagnostic dilemma, and optimal management requires coordinated assessment, timely communication, and shared situational awareness among clinicians, mid-level practitioners, nurses, pharmacists, respiratory therapists, and other allied health professionals. Nursing staff often detect the earliest temperature changes and can provide critical insight into device care, secretion characteristics, skin integrity, stool patterns, and temporal associations with medication administration. Pharmacists contribute by optimizing antibiotic selection and dosing, identifying potential drug fever culprits, and supporting de-escalation strategies that reduce resistance pressures. Infection prevention teams and ICU leadership play a crucial role by implementing and auditing infection control measures, including bundles for ventilator care, central line maintenance, catheter necessity assessment, hand hygiene, and pressure ulcer prevention, thereby reducing the incidence of ICU-acquired infections that frequently manifest as fever. Education of the entire healthcare team, supported by protocolized practices and continuous quality improvement, forms a major strategy for mitigating secondary ICU infections and improving patient outcomes, while also ensuring that fever is evaluated thoughtfully rather than reflexively treated with broad-spectrum antibiotics [56].

Conclusion:

Fever in critically ill patients is neither a trivial nor a uniform clinical sign; it represents a complex physiologic response with diverse etiologies and variable prognostic implications. While infection remains the predominant cause, non-infectious mechanisms—including drug reactions, thromboembolic events, endocrine crises, and neurogenic processes—are frequent and clinically significant. Misattribution of fever solely to infection can lead to indiscriminate antimicrobial use, fostering resistance and delaying recognition of alternative life-threatening conditions. Effective management begins with a structured diagnostic approach that integrates history, physical examination, microbiologic sampling, biomarkers, and imaging, ensuring timely identification of sepsis while avoiding unnecessary interventions. Treatment strategies should prioritize early, appropriate antimicrobial therapy when infection is suspected, coupled with definitive source control. Temperature management must be individualized: permissive fever may be acceptable in stable septic patients, whereas aggressive control is warranted in neurologic injury or extreme hyperthermia. Ultimately, fever should be interpreted within the broader clinical context, serving as a prompt for disciplined evaluation rather than reflexive treatment. Multidisciplinary collaboration, adherence to stewardship principles, and continuous quality improvement are essential to optimize outcomes, reduce complications, and balance the physiologic role of fever against its potential harms in the ICU environment.

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